Evolution of the Genomes of Mammals and Birds

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Comparison of genome maps of mammals suggests that the order of genes on chromosomes tend to be conserved as species evolve. In recent studies we have examined if such conservation is maintained over long periods of evolutionary time by comparing gene maps of birds (namely the chicken), mouse and human. This work led to the remarkable conclusion that the organisation of the human genome is more similar to that of the chicken than mouse.

In the absence of chromosome rearrangements, gene linkage and order are preserved from one generation to the next. During evolution, however, chromosomes break and rejoin and some ancestral linkages are disrupted. The chance that gene arrangements will be conserved between any two species depends on the rate of chromosomal change after divergence from a common ancestor. Closely related species are generally expected to share more conserved segments than distantly related species. However, comparison of the gene maps of chicken and mammals shows that this is not necessarily the case (Burt *et al*., 1999).

Large scale changes in the genome can occur during evolution by translocation, inversions or transpositions of segments of chromosome. By comparing the location of orthologous genes in different species, we can determine whether a chromosomal region has or has not remained intact during evolution. A close sequence homology does not necessarily mean that two genes are orthologous (i.e represent the equivalent gene in different species). Homologous genes can also arise by gene duplication (e.g. the IGF-2 gene by duplication of the insulin gene) and it is important not to confuse such paralogous genes with orthologous genes in comparative analyses.

For comparisons between chicken, pigs, cattle and man, sufficient orthologous genes have been mapped to identify conserved segments (Burt *et al*., 1998; Groenen *et al*., 2000). An example is shown in Figure 1, in which we compare genes mapped to chicken chromosome 3, with human and mouse chromosomes. The result illustrates a common feature of chicken-human-mouse comparisons : that the human-chicken gene arrangements are more similar than human-mouse.

Gene	Chicken		Human	Mouse	
ADPRT	3	75.8	720	1	98.60
TGFB2	3	81.6	704	1	101.50
ACTN2	3	135.7	742	13	7.00
HMX1	3	163.5		5	18.00
T	3	163.5	459	17	4.00
TCP1	3	164.5	620	17	7.50
IGF2R	3	167.6	620	17	7.35
VIP	3	182.2	603	10	S
MYB	3	196.4	545	10	16.00
PLN	3	200.4	495	10	S
FYN	3	210.9	468	10	25.00
CCNC	3	218.0	430	10	S
ME1	3	232.0	367	9	48.00
BMP5	3	250.7	218	9	42.00
GSTA2	3	252.6	199	9	43.00
ODC1	3	279.9	39	12	6.00
MYCN	3	290.5	56	12	4.00

Figure 1. Location of genes on chicken, human and mouse chromosomes showing conservation of gene order. The chromosome numbers are shown together with the location on the genetic maps in chicken and mouse or on the radiation hybrid map of human.

Chromosome rearrangements occur less frequently in chickens than mice

Using comparative maps and a new statistical model of chromosome change (Waddington *et al.*, 2000), we were able to predict that there are 96 conserved segments between the chicken and human genomes, and 152 between chicken and mouse. If we assume that the last common ancestor had 24 chromosomes, our data suggests there have been only 72 chromosome rearrangements between the chicken and human genomes: this is much less than the estimated 128 between mouse and chicken or the 171 between mouse and human.

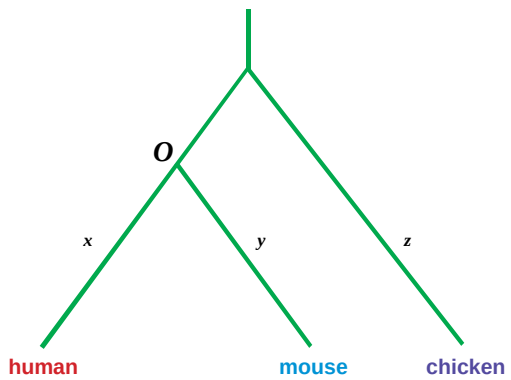

Figure 2. The relative-rate test used to compare the rates of chromosome change in the human (x) and mouse (y) lineages. The diagram shows the rooted tree for human, mouse and chicken, using chicken as the known outgroup. *O*, denotes the common ancestor of human and mouse.

To avoid the problem often associated with uncertainties over dates of species divergence, a relative rate test was used to compare the rates of chromosomal change in human and mouse lineages, using the chicken, as a reference or outgroup species. The findings show (Fig.2) that the number of chromosome rearrangements between human and chicken is equal to the sum of rearrangements that have occurred from point *O* to human (x) and from point *O* to chicken (z). Since we know the number of rearrangements between human-chicken, human-mouse and chicken-mouse, we can determine the number of rearrangements down each lineage. In this way we have shown that since divergence 100 million years ago, the rate of chromosome change in the mouse lineage has been twice as fast as that in the human.

Evolutionary change has slowed in humans

One of the most spectacular approaches to comparing the genomes of different species is the technique of 'chromosomal painting'. DNA complementary to a whole chromosome of one species is labelled with fluorescent dye and hybridised to a chromosomal spread of another species. The probe lights up the chromosomal sections where there is substantial homology (Fig.3).

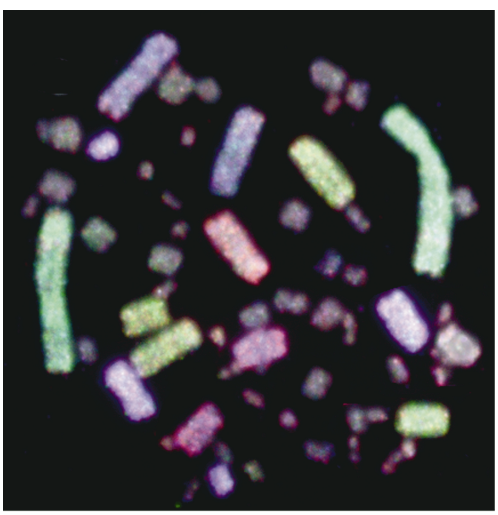

Figure 3. Chromosomal painting of turkey chromosomes with fluorescent probes complementary to chicken chromosomes 1-5. Probes derived from chicken chromosome 2 'paint' two turkey chromosomes. This is not seen in quail, geese or ducks and shows that there has been a break in one of the turkey chromosomes during evolution. *Courtesy of D. Griffin (Brunel University) a member of the EC AVIANOME project.*

We have combined results from genetic mapping, chromosome painting and vertebrate phylogeny (Fig.4) to reveal global patterns of chromosome evolution The rate of chromosome change was slow, less than 0.2 rearrangements per million years in both avian and mammalian lineages between 100-300 million years ago (Mya) (Phase I). The rate increased to over 1.1 rearrangements per million years in both mouse and non-rodent lineages between 65-100 mya (Phase II). During the last 65-85 million years the rate has been very variable in non-rodent mammals (Phase III). Slowest (less than 0.1 rearrangements per My) in human, carnivores and common shrew lineages, higher (0.1-0.3 rearrangements per My) for pig, cattle, horse and dolphin, and highest in the lesser apes (1.5 to 2.3 rearrangements per My).

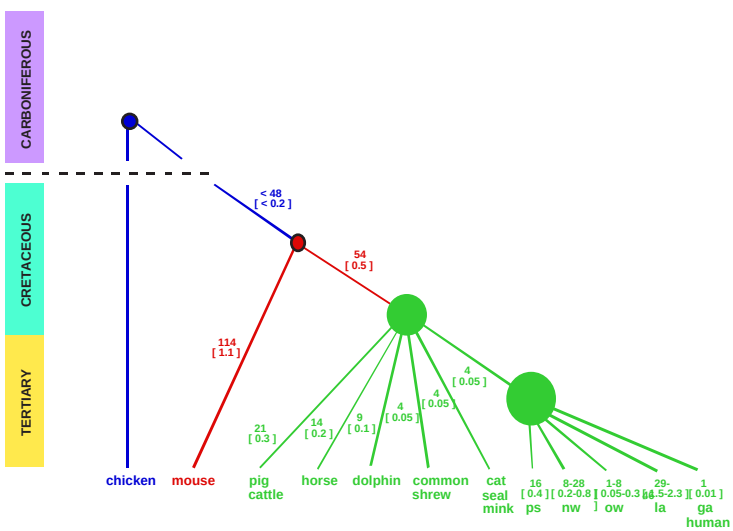

Figure 4. Global patterns of chromosome evolution in birds and mammals. Circles represent estimated times of divergence of common ancestors. The three phases of chromosomal evolution discussed in the text are shown in Blue (Phase I), Red (Phase II) and Green (Phase III). The estimated number of chromosome rearrangements is shown along each lineage, with the rates of chromosomal rearrangement per million years, in brackets. **ps**: Prosimians (Lemur), **nw**: New World Monkeys (six species), **ow**: Old World Monkeys (four species), **la**: Lesser Apes (four species), **ga**: Great Apes (six species).

These findings are similar to those found by comparing the rate at which nucleotide substitutions have taken place in mouse and human genes. Both the rate of chromosome evolution and of which nucleotide substitution appear to be more dependent on generation-time than absolute time, with changes in the mouse being at least twice as fast as that found in humans during the past 100 million years.

Clearly, the rate of evolution in the human lineage during the last 65 million years, has slowed down to one of the lowest in mammals at both the level of the genome (gene order) and the gene (gene sequence).

Practical implications

The relative stability of genomes such as the chicken and human, which span 300 million years of vertebrate evolution, means that it is possible to reconstruct ancestral vertebrate genomes.

The complete sequence of the human genome is expected to be completed within the next 12 months but such a massive effort is currently impractical for vertebrate species other than perhaps the mouse. Studies on farm and other animals are identifying quantitative trait loci containing genes of major effect and comparisons between the genomes of these species with information rich genomes of humans and mice is the most promising way of identifying the genes involved. The results presented here reinforce the evidence that comparative mapping will be applicable to a much wider range of species than initially thought, including species as divergent as human and chickens.

The potential is illustrated by the discovery of a gene involved in sex differentiation in birds (Nanda *et al.*, 1999). Using both genetic and physical mapping methods we found 13 of 19 genes of the chicken Z chromosome to have orthologues on human

chromosome 9pter-q22. The rest of human chromosome 9 shows similarities to chicken microchromosome E41W17 . In mammals, sex is determined by the male-dominant factor SRY on the Y chromosome. Sex-reversal syndromes in humans, however reveal genes on the short arm of chromosome 9 and recently a gene, DMRT1 has been mapped to the critical region.

We predicted that the chicken orthologue of this gene would be located on the Z sex chromosome and be involved in sex differentiation. DMRT1 was indeed mapped to this region and is only expressed in the testis, illustrating that comparative gene mapping can be used as a predictive tool prior to experimental proof.

Acknowledgements

Genome research in the author's laboratory is supported by MAFF, BBSRC, EC and by the poultry breeding industry. The contribution of the many colleagues and collaborators at the Roslin Institute and throughout the world who have contributed to the work described is gratefully acknowledged.

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